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ST elevation myocardial infarction and multi-vessel coronary artery disease: complete or incomplete revascularisation?

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ABSTRACT

The most recent guidelines for the treatment of ST elevation myocardial infarction strongly support a prompt mechanical reopening of the occluded culprit coronary artery. However, there is a great debate regarding how to treat the bystander non-culprit coronary artery disease. While data from retrospective studies and registries suggest that it should be treated in a second-staged procedure, a recent randomised study has suggested a better outcome for patients receiving complete revascularisation during the index primary PCI. In this paper we aim to address this controversial point, analysing the most recent and important scientific publications and trying to give a personal point of view according to the clinical practice in our institution.

Contents

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Introduction

ST elevation myocardial infarction (STEMI) represents the most challenging scenario among the spectrum of acute coronary syndromes: if the urgent flow restoration of the occluded coronary artery significantly reduces complications, decreases mortality and improves outcomes, conflicting data exist regarding the best management of bystander non-culprit lesions.

According to the available literature, the prevalence of significant multi-vessel coronary disease among patients with STEMI varies from 30% to 60% [1–4].

In the following pages we aim to address this controversial point, analysing the most recent and important scientific publications and trying to give a personal point of view according to the clinical practice in our institution.

What do the guidelines say

The 2012 European Society of Cardiology (ESC) guidelines on management of STEMI states that ''Primary percutaneous coronary intervention (PCI) should be limited to the culprit vessel with the exception of cardiogenic shock and persistent ischaemia after PCI of the supposed culprit lesion – Class IIa of recommendation, Level of evidence A'' [5].

The same approach is indicated by the more recent American Heart Association (AHA) guidelines, according to which ''PCI is indicated in a noninfarct artery at a time separate from primary PCI in patients who have spontaneous symptoms of myocardial ischemia (Class I, Level C)''. Lower class of recommendation is given in case of ''patients with intermediate or high-risk findings on noninvasive testing'', for whom ''PCI is reasonable in a noninfarct artery at a time separate from primary PCI (Class IIa, Level C)'' [6].

An important aspect to be taken into account, though, is that the recommendations coming from the cited guidelines are on the basis of retrospective or observational studies, while evidence from randomised studies are poor.

Data from retrospective studies and registries

Multi-vessel PCI in the same setting is worse than single-vessel PCI

To date, the largest dataset comes from the United States National Cardiovascular Data Registry. Cavender et al. [7] retrospectively analysed 31,681 patients with STEMI and multi-vessel coronary disease undergoing primary PCI between 2004 and 2007. The authors compared the outcome of patients undergoing multi-vessel PCI during the index catheterisation ($N = 3134$) with patients undergoing single-vessel PCI of the infarct-related artery (IRA) ($N = 25{,}802$), after excluding patients who underwent staged PCI or left main PCI ($N = 2745$). Of note, the analysis included patients with cardiogenic shock, for whom current guidelines suggest, if possible, complete revascularisation. The overall in-hospital mortality rate was greater in patients undergoing multi-vessel PCI than the single-vessel PCI of the IRA group (7.9% vs. 5.1%, $p < 0.01$). Interestingly, the same result was found considering only the patients with cardiogenic shock, after adjusting for potential confounders (OR 1.54, 95% CI 1.22–1.95, $p < 0.01$). Adjusted analysis for patients without cardiogenic shock failed to prove a statistically significant increased mortality risk in the multi-vessel PCI group vs. the single-vessel PCI group. Similar results come from another STEMI registry, the EUROTRANSFER, a multi-centre European registry [8].

A post hoc analysis of the APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) trial showed that PCI of the significant non-culprit lesion performed in the same setting of the index primary PCI has worse outcomes at 90 days follow-up than a single-vessel PCI of the IRA (12.5 vs. 5.6%, p (log-rank) < 0.001 for death and 17.4 vs. 12.0%, p(log-rank) $= 0.020$ for the composite endpoint of death/CHF/shock).

Different results come from a recently published analysis of the AMIS registry (Acute Myocardial Infarction in Switzerland) [9]. Even if the overall incidence of in-hospital mortality was significantly higher in the multi-vessel PCI group than in the group of single-vessel PCI of the IRA (7.3% vs. 4.4%, $p < 0.001$), this difference disappeared after stratifying patients by risk (22.2% vs. 21.7%, $p = 1.00$ in high-risk patients and 2.0% vs. 2.0% in low-risk patients). Also, the study showed that multi-vessel disease STEMI patients who underwent complete revascularisation were more likely to have a higher risk profile (left-main involvement, out-of-hospital cardiac arrest or higher Killip class).

Staged multi-vessel PCI is better than one-time multi-vessel PCI

If registry data seem to be in favour of a single-vessel PCI of the IRA during the index procedure, a complete revascularisation seems to perform better when performed as a staged procedure.

A retrospective review of the New York State's Percutaneous Coronary Interventions Reporting System analysed 4024 multi-vessel disease patients admitted with STEMI and undergoing primary PCI between 2003 and 2006 [10]. For patients without haemodynamic compromise, a single-vessel PCI of the IRA strategy was associated with lower in-hospital mortality than multi-vessel PCI during the index procedure (0.9% vs. 2.4%, $p < 0.04$). There was a lower mortality rate among patients who underwent staged PCI within 60 days after the index procedure than patients undergoing single-vessel PCI of the IRA.

A recent analysis of a European registry, the Western Denmark Heart Registry, showed that multi-vessel PCI in the acute setting is associated with higher mortality than

multi-vessel PCI performed in a staged fashion within 60 days after the index procedure [11]. Similar results came from a post hoc analysis of the HORIZONS-AMI trial, where multi-vessel PCI in the acute procedure was found to be significantly associated with higher 1-year mortality, cardiac mortality and stent thrombosis than a staged multi-vessel PCI [12].

Staged PCI for significant non-culprit lesions seems to guarantee better outcomes irrespective of when the staged procedure is performed. Indeed, Chen et al. [13] have demonstrated that in 561 multi-vessel disease STEMI patients a staged complete revascularisation significantly reduced 1-year mortality in comparison with single-vessel PCI of the infarct-related artery (OR 0.29, 95% CI 0.15–0.53, $p < 0.0001$). The benefit was present when the staged PCI was performed either early (<1 month from the index procedure) or late (<6 months).

Data from randomised studies

Surprisingly, the data coming from the few randomised studies published so far go against the evidence cited in the previous paragraphs.

A 10-year-old study published by Di Mario et al. [14] showed that a multi-vessel treatment approach in the setting of primary PCI was safe in comparison with the approach of a single-vessel PCI of the IRA, with a similar rate of in-hospital major adverse cardiac events (0% in single-vessel PCI and 3.8% in multi-vessel PCI, p = NS). Nevertheless, the authors observed that, when only the culprit lesion was initially treated, the need for subsequent clinically driven revascularisation remained low and no clinical or economical advantages were obtainable with a more aggressive initial approach. The absence of MACEs in the single-vessel PCI group and the low incidence in the multi-vessel PCI group do not reflect the common clinical practice and are explained by the very small population of the study ($N = 69$).

Politi et al. [15] randomised 214 consecutive patients with STEMI and multi-vessel disease to undergo either complete revascularisation during the index catheterisation, or single-vessel PCI of the IRA or staged multi-vessel PCI and follow them up for 2.5 years. The patients undergoing single-vessel PCI were more likely to experience major adverse cardiac events (MACEs) at follow-up than the other groups (50% vs. 20% vs. 23.1%, $p < 0.001$). No difference in terms of MACEs was observed among patients with multi-vessel PCI, either in the same or in a staged procedure.

In 2013 was presented the ''Randomized Trial of Preventive Angioplasty in Myocardial Infarction'' (PRAMI) [16]. In this multi-centre UK-based trial, the authors enrolled 465 patients with multi-vessel coronary disease undergoing primary PCI. To be considered eligible, patients had to present with one or more stenoses of >50% in the non-culprit artery and had to be suitable either for the preventive or no-preventive approach, according to operator's discretion.

Patients have been randomised to receive either multi-vessel PCI in the same setting of the primary PCI (preventive PCI group, $N = 234$) or infarct-related artery only PCI (no preventive PCI group, $N = 231$). After the randomisation the patients have been followed up for a mean time of 23 months to evaluate the incidence of the primary composite outcome of death from cardiac causes, nonfatal myocardial infarction or refractory angina.

The trial has been stopped prematurely because of the increased incidence of the primary endpoint in the preventive PCI group (HR in the preventive-PCI group, 0.35; 95% confidence interval [CI] 0.21–0.58, $p < 0.001$). The preventive PCI strategy performed better for all the single components of the primary endpoint, except for the cardiac death outcome, where the difference among groups was not statistically significant.

However, several controversial aspects of the trial need to be highlighted. First, the decision of considering eligible a patient was entirely left to operators discretion and that might have caused bias due to inter-observer variability and different personal practice. Before randomisation, 286 patients have been excluded because of the presence of left-main or equivalent disease, chronic total occlusion in the non-infarct artery or due to a failure in re-opening the infarct-related artery (as per study protocol), while 269 patients have been excluded because the non-infarct artery was considered ''unsuitable for PCI''. What are the features that led the operators to judge those arteries not suitable for PCI? Without this information the suspect of the presence of an operator discretion-based bias is high. Second, the authors did not report the distribution of important elements which are well-known predictors of poor prognosis in STEMI (Killip class, anaemia, maximum elevation in enzymes, door-to-balloon time, left ventricular ejection fraction, and creatinine level) [17]. Third, there are no details regarding the characteristics of the coronary lesions in the non-culprit arteries (a critical stenosis left in the proximal left anterior descending artery has worse prognosis in comparison with a critical stenosis in the distal right coronary artery) [18]. Fourth, no data are available regarding the outcome of the non-invasive functional tests performed in 81 patients of the no preventive PCI group and in 39 patients of the preventive PCI group. Fifth, a careful look to the medical treatment reveals that the majority of patients had just one single anti-ischaemic agent (mainly beta-blockers). Since one of the endpoint was the presence of refractory angina, it is possible that not all the patients have been treated with optimal anti-anginal medical treatment. Finally, the strategy proposed by PRAMI seems to be unfeasible in the daily practice, especially in high-volume centres. Indeed, performing a multi-vessel PCI can significantly increase the duration of the procedure and that might represent an issue in case of other impending emergencies. This is especially true during the night shifts, where the on-call team's performance can be lower and the back-up in case of complications might be sub-optimal.

In conclusion, PRAMI has the indisputable merit to be the biggest trial trying to address a topic for which very few randomised data are available. Nevertheless, we believe that, in presence of bystander angiographically significant coronary artery disease, the option of medical treatment only is not appropriate. It does not reflect the common clinical practice, where, if doubts regarding bystander lesions arise during the index procedure, patients are sent for functional tests to assess inducible ischaemia rather than being left on medical treatment alone.

Data from meta-analyses

In 2011 Vlaar et al. retrospectively reviewed 40,280 cases with STEMI and multi-vessel coronary artery disease undergoing PCI. The following strategies have been evaluated: (1) IRA only PCI, (2) multi-vessel PCI in the index procedure and (3) staged PCI for the significant non-culprit lesions. The authors reported a clear benefit for the staged PCI strategy as regards the primary endpoint of short-term mortality, compared with the single-vessel PCI of the IRA strategy (OR: 3.03, 95% CI 1.41–6.51, $p < 0.005$) and with the multi-vessel PCI strategy (OR: 5.31, 95% CI 2.31–12.21, $p < 0.0001$) [19].

A more recent meta-analysis confirmed this concept; in case of STEMI and multi-vessel disease, a complete revascularisation strategy during the primary PCI was associated with an increased in-hospital mortality (OR 1.35, 95% CI 1.19–1.54, $p < 0.001$). On the contrary, a multi-vessel PCI performed in a staged-fashion resulted in a reduced in-hospital mortality (OR 0.35, 95% CI 0.21–0.59, $p < 0.001$; p interaction <0.001) [20].

Importantly, the above-discussed meta-analyses did not include PRAMI results.

Our personal point of view

Finding the best treatment in the STEMI setting is challenging.

The presence of more potent antithrombotic agents along with a more diffuse adoption of the radial approach to reduce bleeding, opens new options to improve patients' outcomes. As regards the culprit lesion, the clinical context of STEMI and the extensive thrombotic burden may require a combination of mechanical and aggressive pharmacological approach. The recently published DEFER-STEMI trial [21] has proven an

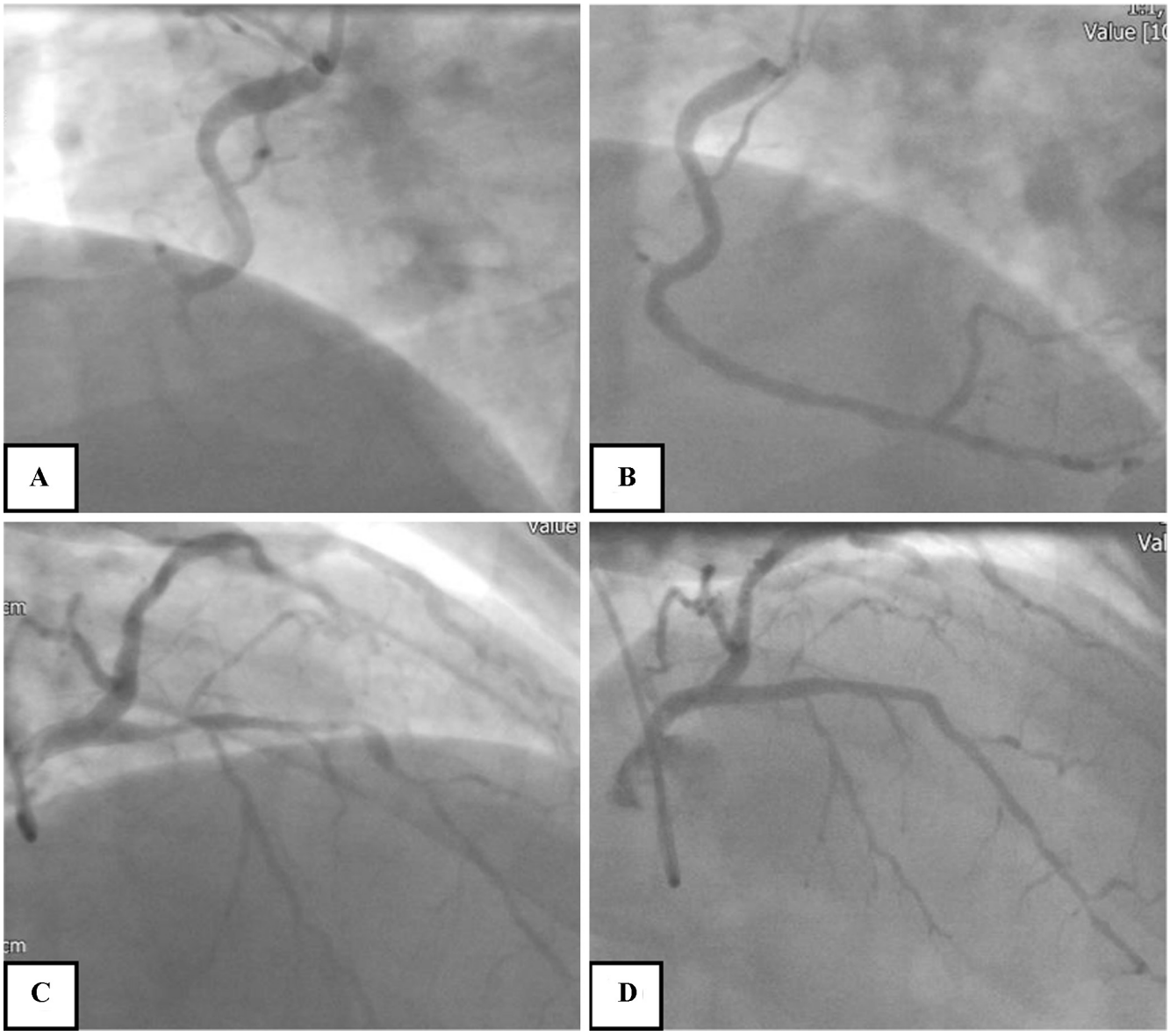

Fig. 1 – A 52-year-old man admitted with an inferior ST elevation myocardial infarction underwent a successful primary PCI to his right coronary artery (panels A and B). A bystander critical stenosis in the mid left anterior descending artery was then successfully treated with a staged PCI 5 days later after the index presentation (panels C and D).

Table 1 – Ongoing randomised studies in STEMI patients with multi-vessel PCI.[a]

CVLPRIT (UK)	N = 300	Complete in-hospital revascularisation versus culprit only + conservative strategy
PRAGUE-13 (Czech Republic)	N = 400	Complete staged revascularisation versus culprit only + conservative strategy
CROSS-AMI (Spain)	N = 400	Complete staged revascularisation versus culprit only + stress echo guided revascularisation
COCUA (Korea)	N = 646	Complete acute revascularisation versus culprit only + staged revascularisation strategy
COMPARE-ACUTE (Europe and Asia)	N = 885	FFR guided complete (sub) acute revascularisation versus culprit only + conservative strategy
DANAMI-III (Denmark)	N = 2000	3 × 2 factorial design – culprit vessel PCI with DES versus culprit vessel thrombectomy with balloon angioplasty – primary PCI with or without post-conditioning – complete revascularisation versus culprit only
COMPLETE (USA and Canada)	N = 3900	Complete revascularisation (acute or staged) versus culprit only + conservative strategy

[a] Reprinted from Smits [27], with permission from Europa Digital & Publishing.

interesting concept. The authors have demonstrated that, after the mechanical flow restoration in the culprit artery, leaving the patients on GpIIb/IIIa inhibitors + low molecular weight heparin and deferring stenting in a second-staged procedure reduced the risk of no-reflow and increased the myocardial salvage in comparison with an immediate stenting strategy. Nevertheless, 2 out of 52 patients in the deferred PCI group experienced a re-occlusion of the infarct-related artery and this outcome highlights the major limitation of this strategy.

As regards the non-culprit lesions, if a complete revascularisation before the discharge seems to be an obvious strategy in case of a patient with a critical bystander proximal LAD stenosis and long-standing history of angina preceding the myocardial infarction (Fig. 1), the choice becomes more difficult in case of intermediate bystander coronary artery disease in patients with no previous cardiac history or symptoms. The key decisional factor in the latter case is represented, in case of asymptomatic patients, by the proof of inducible ischaemia on functional tests, where the PCI option is superior to medical treatment only [22].

The decision is even more challenging because the visual angiographic inspection has been demonstrating its weakness as a predictor of either the functional significance or subsequent cardiovascular events in asymptomatic patients.

The FAME trial (Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention) [23] has demonstrated the superiority of the fractional flow reserve-guided approach over the angiographic-guided approach in stable patients with multi-vessel coronary artery disease; 2-year rates of mortality or myocardial infarction were 12.9% in the angiography-guided group and 8.4% in the FFR-guided group ($p < 0.02$). Interestingly, 37% of the lesions judged significant on the angiographic assessment (>50% of stenosis) had an FFR of less than 0.80.

An FFR-guided approach for non-culprit lesions in primary PCI and multi-vessel coronary artery disease could be a feasible and valid approach but needs to be validated by big randomised trials [24,25].

As shown by Stone et al. in the PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) [26], over a follow-up of 3 years, only the 11.6% of 697 patients with acute coronary syndrome and bystander coronary artery disease developed a subsequent major adverse cardiovascular event caused by any of the non-culprit lesions. More importantly, the majority of these lesions were mild (less than 30% stenosis) on the basis of visual assessment at the index angiography.

In our centre, the treatment for STEMI patients with multivessel coronary artery disease does not differ from what is recommended by the current guidelines and follows a careful ''patient-tailored'' approach. Excluding the very complex cases with cardiogenic shock, we do not tend to perform a multivessel PCI during the index catheterisation, where we ''just'' aim to restore flow in the culprit artery and stabilise the culprit lesion.

The following step to treat bystander coronary artery disease can be either completing the revascularisation during the index hospitalisation, re-assessing the angina burden at an early follow-up visit or, if needed, performing a functional test in order to guide any further intervention.

Future perspectives

Several ongoing randomised studies (Table 1) will definitely provide a great contribution to this topic [27]. Hopefully, they will give an answer to the current unmet needs in the treatment of STEMI patients with multi-vessel coronary artery disease.

Conflict of interest

The authors have no relevant conflict of interest to declare.

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Ethical statement

This research was done according to ethical standards.

REFERENCES

[1] J.A. Goldstein, D. Demetriou, C.L. Grines, et al., Multiple complex coronary plaques in patients with acute myocardial infarction, The New England Journal of Medicine 343 (2000) 915–922.

[2] S.-G. Lee, C.W. Lee, M.-K. Hong, et al., Change of multiple complex coronary plaques in patients with acute myocardial infarction: a study with coronary angiography, American Heart Journal 147 (2004) 281–286.

[3] R.A. Corpus, J.A. House, S.P. Marso, et al., Multivessel percutaneous coronary intervention in patients with multivessel disease and acute myocardial infarction, American Heart Journal 148 (2004) 493–500.

[4] E.L. Hannan, Z. Samadashvili, G. Walford, et al., Staged versus one-time complete revascularization with percutaneous coronary intervention for multivessel coronary artery disease patients without ST-elevation myocardial infarction, Circulation: Cardiovascular Interventions 6 (2013) 12–20.

[5] Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology (ESC), P.G. Steg, S.K. James, et al., ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, European Heart Journal 33 (2012) 2569–2619.

[6] Writing Committee Members, P.T. O'Gara, F.G. Kushner, et al., 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, Circulation 127 (2013) e362–e425.

[7] M.A. Cavender, S. Milford-Beland, M.T. Roe, et al., Prevalence, predictors, and in-hospital outcomes of non-infarct artery intervention during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (from the National Cardiovascular Data Registry), The American Journal of Cardiology 104 (2009) 507–513.

[8] A. Dziewierz, Z. Siudak, T. Rakowski, et al., Impact of multivessel coronary artery disease and noninfarct-related artery revascularization on outcome of patients with ST-elevation myocardial infarction transferred for primary percutaneous coronary intervention (from the EUROTRANSFER Registry), The American Journal of Cardiology 106 (2010) 342–347.

[9] M. Jaguszewski, D. Radovanovic, B.K. Nallamothu, et al., Multivessel versus culprit vessel percutaneous coronary intervention in ST-elevation myocardial infarction: is more worse, EuroIntervention 9 (2013) 909–915.

[10] E.L. Hannan, Z. Samadashvili, G. Walford, et al., Culprit vessel percutaneous coronary intervention versus multivessel and staged percutaneous coronary intervention for ST-segment elevation myocardial infarction patients with multivessel disease, JACC: Cardiovascular Interventions 3 (2010) 22–31.

[11] L.O. Jensen, P. Thayssen, D.K. Farkas, et al., Culprit only or multivessel percutaneous coronary interventions in patients with ST-segment elevation myocardial infarction and multivessel disease, EuroIntervention 8 (2012) 456–464.

[12] R. Kornowski, R. Mehran, G. Dangas, et al., Prognostic impact of staged versus one-time multivessel percutaneous intervention in acute myocardial infarction, Journal of the American College of Cardiology 58 (2011) 704–711.

[13] H.-C. Chen, T.-H. Tsai, H.-Y. Fang, et al., Benefit of revascularization in non-infarct-related artery in multivessel disease patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention, International Heart Journal 51 (2010) 319–324.

[14] C. Di Mario, S. Mara, A. Flavio, et al., Single vs multivessel treatment during primary angioplasty: results of the multicentre randomised HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction (HELP AMI) Study, Int J Cardiovasc Intervent 6 (2004) 128–133.

[15] L. Politi, F. Sgura, R. Rossi, et al., A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: major adverse cardiac events during long-term follow-up, Heart 96 (2010) 662–667.

[16] D.S. Wald, J.K. Morris, N.J. Wald, et al., Randomized trial of preventive angioplasty in myocardial infarction, The New England Journal of Medicine 369 (2013) 1115–1123.

[17] R. Shah, M.R. Khan, K. Matin, Preventive angioplasty in myocardial infarction, The New England Journal of Medicine 370 (2014) 281–282.

[18] J.-G. Dillinger, G. Sideris, P. Henry, Preventive angioplasty in myocardial infarction, The New England Journal of Medicine 370 (2014) 280–281.

[19] P.J. Vlaar, K.D. Mahmoud, D.R. Holmes, et al., Culprit vessel only versus multivessel and staged percutaneous coronary intervention for multivessel disease in patients presenting with ST-segment elevation myocardial infarction: a pairwise and network meta-analysis, Journal of the American College of Cardiology 58 (2011) 692–703.

[20] K.R. Bainey, S.R. Mehta, T. Lai, R.C. Welsh, Complete vs culprit-only revascularization for patients with multivessel disease undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: a systematic review and meta-analysis, American Heart Journal 167 (2014), 1–14.e2.

[21] D. Carrick, K.G. Oldroyd, M. McEntegart, et al., A randomized trial of deferred stenting versus immediate stenting to prevent no- or slow-reflow in acute ST-segment elevation myocardial infarction (DEFER-STEMI), Journal of the American College of Cardiology 63 (2014) 2088–2098.

[22] P. Erne, A.W. Schoenenberger, D. Burckhardt, et al., Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial, The Journal of the American Medical Association 297 (2007) 1985–1991.

[23] P.A.L. Tonino, B. De Bruyne, N.H.J. Pijls, et al., Fractional flow reserve versus angiography for guiding percutaneous coronary intervention, The New England Journal of Medicine 360 (2009) 213–224.

[24] A. Ntalianis, J.W. Sels, G. Davidavicius, et al., Fractional flow reserve for the assessment of nonculprit coronary artery stenoses in patients with acute myocardial infarction, JACC: Cardiovascular Interventions 3 (2010) 1274–1281.

[25] J.-H.E. Dambrink, J.P. Debrauwere, A.W.J. van't Hof, et al., Non-culprit lesions detected during primary PCI: treat invasively or follow the guidelines? EuroIntervention 5 (2010) 968–975.

[26] G.W. Stone, A. Maehara, A.J. Lansky, et al., A prospective natural-history study of coronary atherosclerosis, The New England Journal of Medicine 364 (2011) 226–235.

[27] P.C. Smits, STEMI patients and non-culprit lesions: what to do and when? EuroIntervention 9 (2013) 895–897.